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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,925	01/31/2001	Steven Neville Chatfield	117-320	2850

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EXAMINER
FORD, VANESSA L

ART UNIT	PAPER NUMBER
1645	14

DATE MAILED: 12/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,925	CHATFIELD, STEVEN NEVILLE	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the c rresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *12 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-11 and 13 and clinical study reports filed on September 30, 2002 are acknowledged. Claims 12 and 14-16 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The traversal is on the grounds that Groups I-IV are not independent and distinct, therefore the examination of the entire application or at least Groups I-IV share the same special technical feature. These arguments have been fully considered but are not found to be persuasive for the reasons below:

MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example as product and method of use, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable over each other (see MPEP 802.01). In the instant situation, the inventions of Groups I-IV are drawn to two different patentably distinct inventions which are separate products capable of separate manufacture, use or sale as described in the previous Office Action.

Novelty of the instant invention appears to be a bacterium that attenuated by a non-reverting mutation in each of the aroC gene, the ompF gene and the ompC gene. Applicant asserts that "such bacteria" make a contribution of the prior art". The inventions listed as Groups I-V do not relate to a single general inventive concept under

PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Chatfield et al, *(Infection and Immunity, January 1991, p. 449-452)* teach a *Salmonella typhimurium* strain (SL1344) harboring stable mutations in both *ompC* and *ompF* (see the Abstract). Chatfield et al teach that the *ompC* and *ompF* double mutants of *Salmonella typhimurium* are useful as attenuated orally but shows little loss of virulence when given intravenously (see page 451, 2nd column). Chatfield et al do not teach a mutant in the *aroC* gene. However, Dougan et al, (*The Journal of Infectious Diseases, Vol. 158, No.6, December 1988)* teach mutations in the *aroC* and *aroA* gene of *Salmonella typhimurium* strain (SL3144). Dougan et al teach that fifty percent lethal doses after intravenous inoculation of mutants into BALB/C mice were determined and the *aroC* mutants were as highly attenuated as were the *aroA* mutants (see the Abstract). It would have been obvious at the time the invention was made to add the *aroC* mutants as taught by Dougan et al to the *ompC* and *ompF* mutants of Chatfield et al because Dougan et al teach that mutations in *aroC* genes are were highly attenuated after intravenous inoculation (see the Abstract).

Therefore, Group I is the main invention in this application and it lacks novelty, therefore the other claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept and the invention does not make a contribution over the prior art.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-11 and 13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-11 and 13 are drawn to a bacterium attenuated by a non-reverting mutation in each of the aroC gene, the ompF gene and the ompC gene.

Because it is not clear that cell lines possessing the properties of the Enterotoxigenic *Escherichia coli* strain E1392/75/2A are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the claims require the use of a suitable deposit for patent purposes a deposit in a public repository is required. Without a publicly available deposit of the above Enterotoxigenic *Escherichia coli* strain E1392/75/2A, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell line is an unpredictable event.

Applicant's referral to the Enterotoxigenic *Escherichia coli* strain E1392/75/2A on pages 15-28 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by the International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application. These requirements are necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

> (a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in the public repository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the repository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;
2) The name and address of the depositor;
3) The date of deposit;
4) The identity of the deposit and the accession number given by the depository;
5) The date of the viability test;
6) The procedures used to obtain a sample if test is not done by the depository; and
7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a

position to corroborate that the Enterotoxigenic *Escherichia coli* strain E1392/75/2A described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed. Applicant's attention is directed to In re Lundack, 773 F.2d.1216, 227 USPQ (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-8, 10-11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Charles et al *(U.S. Patent No. 5,683,700, published November 4, 1997)* in view of Chatfield et al *(Infection and Immunity, January 1991, p. 449-452).*

Claims 1-8, 10-11 and 13 are drawn to a bacterium attenuated by a non-reverting mutation in each of the aroC gene, the ompF gene and the ompC gene.

Charles et al teach attenuated *Salmonella* bacteria which capable of expressing a heterologous protein, the expression of the heterologous protein being under the

control of a promoter (i.e. the nirB promoter) whose activity is induced by anaerobic conditions and the attenuated bacterium can be used as a vaccine (see the Abstract). Charles et al teach that the attenuated bacterium may be selected from the genera *Salmonella, Bordetella, Vibrio, Haemophilis, Neisseria, Yersinia* and alternatively the attenuated bacterium may be an attenuated strain of Enterotoxigenic *Escherichia coli* (column 2). Charles et al teach an attenuated bacterium that harbors a non-reverting mutation in a gene conserved with regulation or responses to environmental stimuli (i.e. ompR gene) and the bacterium also harbors a second mutation in a gene that is involved in a essential biosynthetic pathway (i.e. aroC gene) (column 2). Charles et al teach that the attenuated bacterium can harbor a non-reverting mutation from two discrete aromatic amino acid pathway (i.e. double aro mutants)(column 2). Charles et al teach that the heterologous protein expressed in the host and induces in the host an immune response against the microorganism (see the Abstract). Charles et al teach immunization of BALB/c mice using the vaccines of the invention comprising ompR gene and aro gene mutations (columns 7-8).

Charles et al do not specifically teach mutations in the ompC and ompF genes of a bacterium.

Chatfield et al teach a *Salmonella typhimurium* strain (SL1344) harboring stable mutations in both *ompC* and *ompF* (see the Abstract). Chatfield et al teach that the *ompC* and *ompF* double mutants of *Salmonella typhimurium* are useful as attenuated orally but shows little loss of virulence when given intravenously (see page 451, 2nd

column). Chatfield et al teach that mutations in either the ompC or ompF did not lead to attenuation of *Salmonella* virulence (page 449, 1st column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the attenuated *Salmonella* bacterium comprising ompR and aro mutants as taught by Charles et al by substituting the *ompC* and *ompF* mutants of Chatfield et al for the ompR mutants because Chatfield et al teach that ompR mutants are highly pleiotropic whereas mutations in the ompC and the ompF structural genes are specific (page 450, 2nd column) and Chatfield et al also teach that ompC ompF double mutants appear highly attenuated when given by oral or intravenous route, but show little loss of virulence when administered intraperitoneally (page 451, 1st column). It would be expected barring evidence to the contrary that a bacterium comprising the ompC and ompF mutants of Chatfield et al and the aro double mutants (i.e. mutations in the aroA and aroC genes) as taught by Charles et al would be use in a vaccine composition that is highly attenuated and non-reverting when administered to a subject because Chatfield et al teach that bacterium harboring the ompC and ompF mutants are highly attenuated and Charles et al teach that bacterium harboring a non-reverting mutation in a gene conserved with regulation or responses to environmental stimuli and a gene harboring a second mutation in a gene in the biosynthesis pathways are non-reverting (i.e. can not revert to the virulent state) attenuated bacteria which can be used as vaccines (column 2).

4. Claims 1-5, 7-11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Charles et al *(WO 92/15689, published September 17, 1992).* in view of Chatfield et al *(Infection and Immunity, January 1991, p. 449-452).*

Claims 1-5, 7-11 and 13 are drawn to a bacterium attenuated by a non-reverting mutation in each of the aroC gene, the ompF gene and the ompC gene.

Charles et al teach attenuated *Salmonella* bacteria which capable of expressing a heterologous protein, the expression of the heterologous protein being under the control of a promoter (i.e. the nirB promoter) whose activity is induced by anaerobic conditions and the attenuated bacterium can be used as a vaccine (see the Abstract). Charles et al teach that the attenuated bacterium may be selected from the genera *Salmonella, Bordetella, Vibrio, Haemophilis, Neisseria, Yersinia* and alternatively the attenuated bacterium may be an attenuated strain of Enterotoxigenic *Escherichia coli* (page 3). Charles et al teach an attenuated bacterium that harbors a non-reverting mutation in a gene conserved with regulation or responses to environmental stimuli(i.e. ompR gene) and the bacterium also harbors a second mutation in a gene that is involved in a essential biosynthetic pathway (i.e. aroC gene) (page 4). Charles et al teach that the non-reverting mutations may be a deletion, insertion, inversion or substitution and that the deletion mutation may be generated using a transposon (page 4). Charles et al teach immunization of BALB/c mice using the vaccines of the invention comprising ompR gene and aro gene mutations (pages 12-13).

Charles et al do not specifically teach mutations in the ompC and ompF genes of a *Salmonella* bacterium.

Chatfield et al teach a *Salmonella typhimurium* strain (SL1344) harboring stable mutations in both *ompC* and *ompF* (see the Abstract). Chatfield et al teach that the *ompC* and *ompF* double mutants of *Salmonella typhimurium* are useful as attenuated orally but shows little loss of virulence when given intravenously (see page 451, 2nd column). Chatfield et al teach that mutations in either the ompC or ompF did not lead to attenuation of *Salmonella* virulence (page 449, 1st column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the attenuated *Salmonella* bacterium comprising ompR and aro mutants as taught by Charles et al by substituting the *ompC* and *ompF* mutants of Chatfield et al for the ompR mutants because Chatfield et al teach that ompR mutants are highly pleiotropic whereas mutations in the ompC and the ompF structural genes are specific (page 450, 2nd column) and Chatfield et al also teach that ompC ompF double mutants appear highly attenuated when given by oral or intravenous route, but show little loss of virulence when administered intraperitoneally (page 451, 1st column). It would be expected barring evidence to the contrary that a bacterium comprising the ompC and ompF mutants of Chatfield et al and the aro mutants (i.e. mutations in the aroC gene) as taught by Charles et al would be use in a vaccine composition that is highly attenuated and non-reverting when administered to a subject because Chatfield et al teach that bacterium harboring the ompC and ompF mutants are highly attenuated and Charles et al teach that bacterium harboring a non-reverting mutation in a gene conserved with regulation or responses to environmental stimuli and harboring a second mutation in a gene in the biosynthesis pathways are non-reverting

(i.e. can not revert to the virulent state) attenuated bacteria which can be used as vaccines (page 4).

Pertinent Prior Art

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure *(Nogami et al, Journal of Bacteriology, November 1985, p. 797-801).*

Status of Claims

6. No claims are allowed.

Conclusion

7. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
December 7, 2002